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EXAMINER	
MCGAW, MICHAEL M	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,841	GEERLIGS ET AL.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *17-19* is/are withdrawn from consideration.

5)☒ Claim(s) *14* is/are allowed.

6)☒ Claim(s) *1-13 and 15-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/02/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-16, drawn to a vaccine against Newcastle Disease virus, classified in class 424, subclass 214.1.

II. Claims 17-19, drawn to an assay kit, classified in class 435, subclass 5.

The inventions are distinct, each from the other because of the following reasons: Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions involve a vaccine against Newcastle Disease virus and an assay kit having a different mode of operation from the vaccine and not requiring the same particular features of the claimed vaccine.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with John F. Levis on Wednesday, April 14, 2004 a provisional election was made to prosecute the invention of Invention I, claims 1-16. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112, ¶1

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 defines its product in terms of that to which it is lacking, namely a binding site for the monoclonal antibody designated mAb 54. Therefore, mAb 54 is essential to make and use the invention, since mAb 54 is critical to define what is missing. Applicant has not adequately disclosed how to obtain this antibody in the specification. Most particularly, applicant has not indicated the availability of this antibody to the public. There is no teaching in the specification describing the structural features of the antibody. Applicant, on page 5 of the disclosure, points to Collins, M.S., *Arch. Virol.*

(1989) **104**:53-61 as describing the characterization of Mab 54. However, while Collins et al. teach that the antibody binds to the Newcastle disease virus, there is no indication that the antibody binds to the particular region of the F protein claimed. Nor does the reference provide a repeatable method to obtain the antibody. Therefore, it is determined that the skilled artisan would be unable to make the antibody claimed. Claims 2-6 are dependent upon this claim. Likewise, claims 8-13 either recite the use of mAb 54 or are dependent upon a claim reciting mAb54.

Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6 and 7 are directed to a mutant immunogen "identified as p. 13... deposited at the CNCM in Paris, France under accession number # I-2928."

As outlined above in the context of mAb 54, these claims require the use of specific biological materials. As a required element of enablement such biological material must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by the deposit of the antibody and the virus strain recited in the claims. See CFR 1.802. The specification does not provide a repeatable method for obtaining these materials and it is not apparent that they are readily available the public.

Applicant's deposit statement on page 3 of the specification does not indicate the extent of public availability. If the deposit is made under the terms of the Budapest treaty, then an affidavit or declaration by the applicant, or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit is made under terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808. In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See CFR 1.803 through 1.809.

Claims 3, 4, 5 and 12 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A literal reading of claim 12, assuming claim 12 is dependent upon independent claim 10, would indicate that the mutant immunogen is actually generated during growth in the embyronated eggs. Neither the prior art nor the present disclosure teach propagating virus in the presence of antibodies in eggs. One threshold question of such a proposal would be whether the even distribution of antibody within the egg could be ensured.

In example 2 on page 11 of the specification it indicates that the mutants were generated and selected via immunoselection of variant plaques. Such a technique would allow for an even distribution of antibody and would have the added benefit that the practitioner could be fairly sure that an isolated plaque corresponded to a single mutation. In the absence of such a plaque purification system the population of mutants would be much more likely to be heterogeneous.

Yusoff, K., et.al., *J. gen. Virol.* (1989) **70**, 3105-3109 also employ the technique of immunoselection of variant plaques to generate escape mutants of ND virus. See page 3106. They do not indicate how one would generate escape mutants of ND virus by growth in eggs.

Claims 3, 4 and 5 are drawn to the serial passaging of the virus in poultry eggs. Page 12 of the specification speaks of "[g]rowth of repassaged virus from each plaque in VERO cells with and without mAb 617/54." It is not clear to the examiner whether the presence of mAb 54 is a requirement during repassage. If it is needed during the serial passaging in embryonated eggs, then an issue similar to that raised immediately above for claim 12 would arise; namely, how does one ensure the distribution of antibody in the egg such that the virus grows in the presence of antibody? Or, is the virus being passaged through the eggs simply for scale up of virus as indicated on page 6, line 16 of the specification?

In conclusion, due to the claims requiring that the vaccine be propagated in eggs with antibody, the lack of direction in the disclosure and the prior art for making a vaccine by growing virus with an antibody in eggs, the lack of working examples

demonstrating the technique, the lack of predictability of the skilled artisan for how to make that which was never taught, it is determined that an undue quantity of experimentation would be required to make the instant vaccine claimed.

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 7, 11, 12, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 states in relevant part "said serial passaging comprises ***at least about*** two and ***up to about*** ten serial passages." (emphasis added) In the context of a very limited range of finite integers the phrase "at least about" renders the scope of the claim indefinite. For instance, 1 would be about 2 passages, but it would not be at least 2 passages.

Likewise, when claim 5 states "said serial passaging comprises about four to about six serial passages", the claim becomes vague in the context of such a small range of possible passage numbers.

Claim 7 is directed to "[a]n immunogen of Newcastle Disease virus having the ***immunogenic characteristics*** of the strain deposited..." (emphasis added). Likewise, claim 15 refers to unenumerated "immunogenic characteristics." It is not clear from the disclosure exactly what immunogenic characteristics to which the applicant refers. Does the applicant mean that the deposited strain shares all of the immunogenic

characteristics of the NDW vaccine strain minus the immunodominant A4 epitope of the F glycoprotein as recognized by mAb 54?

Claims 11 and 12 both depend upon themselves. For instance, claim 11 begins with the preamble "The method of claim 11, wherein..." Likewise, claim 12 begins with the preamble "The method of claim 12, wherein..."

Claim 16 is drawn to "[a] mutant immunogen of Newcastle Disease virus in which the amino acid serine is replaced by arginine at position 157." While one might reasonably assume that applicant is referring to the F glycoprotein, other ND virus proteins have amino acid sequences containing a position 157, rendering the scope of this claim vague.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Yusoff. Yusoff, K., et.al., *J. gen. Virol.* (1989) **70**, 3105-3109.

Claim 10 is drawn to a method of generating a Newcastle Disease virus mutant immunogens by growing Newcastle Disease virus in the presence of a monoclonal antibody (designated mAb 54 and directed against a specific antigenic binding site on

the F glycoprotein), such that the mutant develops and grows in the presence of the monoclonal antibody whereas nonmutants are neutralized by the monoclonal antibody.

Yusoff also teaches a method of generating a Newcastle Disease virus mutant immunogens produced by growing Newcastle Disease virus in the presence of a monoclonal antibody (designated mAb U79 and directed against a specific antigenic binding site - the immunodominant A4 epitope) such that the mutant develops and grows in the presence of the monoclonal antibody whereas nonmutants are neutralized by the monoclonal antibody. See pg. 3106.

Both mAb 54 and MAb U79 induced a change in the serine amino acid at position 157 of the F glycoprotein, leading to the firm conclusion that these are both directed against the immunodominant A4 epitope and appear to be analogous antibodies. Where, as here, the Patent Office lacks the facilities to perform comparisons between the claimed material and prior art materials that reasonably appear to meet the claim limitations, the burden is properly shifted to applicant to distinguish the claimed product from the prior art product. See In re Best, Bolton, and Shaw, 195 USPQ 430 (CCPA 1977); Ex Parte Gray, 10 USPQ2nd 1922 (BPAI 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mebatsion (WO 02/36617 A2) in view of Yusoff, K., et.al., *J. gen. Virol.* (1989) **70**, 3105-3109. See also Peeters (WO99/66045 and 6,719,979 B2).

Claim 1 is drawn to a vaccine against Newcastle Disease virus based upon a mutant immunogen derived from the NDW vaccine strain of Newcastle disease virus where the mutant immunogen is distinguishable from the vaccine strain, and other wild type viruses, by the loss of the antigenic binding site on the F glycoprotein due to the substitution of the amino acid serine at position 157. Applicant's mutant immunogen can thus be used as a vaccine, which can be serologically distinguished from a natural infection with NDV by the absence of binding by a certain monoclonal antibody. Claim 2 is drawn to the propagation of the vaccine via passaging. Claims 3-5 are drawn to passaging the virus in poultry eggs for propagation.

Mebatsion also describes a whole virus based ND marker vaccine where the marker strain is distinguished by the loss of an immunodominant epitope. In particular. Mebatsion discloses a vaccine against Newcastle Disease virus based upon a mutant immunogen derived from Newcastle disease virus where the mutant immunogen is distinguishable from the vaccine strain, and other wild type viruses, by the loss of the antigenic binding site on the nucleoprotein (NP) due to the deletion of a series of amino acids.

Mebatsion provided the impetus for the creation of his invention when he stated that "all currently used whole virus based live and inactivated ND vaccines have a major

drawback, in that vaccinated animals cannot be distinguished from infected animals with standard serologic tests...Therefore, there is a need for NDV immunogenic material comprising a NDV protein lacking at least one immunodominant epitope." See page 1. While not limiting the disclosure to any specific strain, Mebatsion pointed out that NDV mutants such as that disclosed could be derived from any conventional ND vaccine strain. Also offered were examples of such suitable NDV vaccine strains available at the time, including the NDW vaccine strain. See page 8. Mebatsion pointed out that a whole virus based ND marker vaccine should focus on either the NP or F proteins, where these proteins retain their native form. See page 3. Mebatsion also discusses the desirability of altering the immunodominant epitope by substitution, rather than deletion, presumably to achieve a protein retaining its native form to the greatest extent possible while simultaneously ablating the targeted immunodominant epitope. See page 8. Lastly, Mebatsion teaches the propagation of the ND marker vaccine by passage in either tissue culture, including chicken embryo fibroblasts, or in embryonated eggs. See page 9.

Mebatsion does not teach the loss of the antigenic binding site on the F glycoprotein due to the substitution of the amino acid serine at position 157. Rather, Mebatsion's invention was directed at the NP protein.

Yusoff does teach the loss of the antigenic binding site on the F glycoprotein due to the substitution of the amino acid serine at position 157. Yusoff demonstrated the creation of escape mutants of ND virus where these mutants are created by propagating the virus in the presence of a single neutralizing monoclonal antibody. One

of the mutants created was a mutant ND virus where the mutant was serologically distinguishable from the wild type ND virus through the loss of an immunodominant epitope on the F glycoprotein due to the substitution of the amino acid serine at position 157. Furthermore, Yusoff was able to show that this particular escape mutant retained the ability to bind other antibodies binding outside of the A4 epitope. See Table 2.

One of ordinary skill in the art would have had a reasonable expectation of success of combining the mutant ND marker vaccine taught by Mebatsion with the escape mutant as taught by Yusoff to generate an ND marker vaccine distinguishable from wild type virus, and other vaccine strains, by the loss of the antigenic binding site on the F glycoprotein due to the substitution of the amino acid serine at position 157. Such a change would have the desirable feature, as indicated by Mebatsion, of creating the least disturbance to the native form of the protein of interest while simultaneously ablating the targeted immunodominant epitope.

Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mebatsion and Yusoff as applied to claims 1-6 above, and further in view of van Wiltenburg (5,149,530).

Claim 8 is drawn to a method of protecting a poultry animal from Newcastle Disease via administration of $10^0 - 10^9$ EID_{50} of a mutant NDW strain of ND virus where the mutant immunogen lacks the antigenic binding site on the F glycoprotein due to the

substitution of the amino acid serine at position 157. Claim 9 differs from claim 8 by establishing a narrower range for the concentration at $10^4 - 10^9$ EID_{50}.

The combined teachings of Mebatsion and Yusoff, as more fully outlined above, provide a mutant immunogen wherein said mutant immunogen lacks the antigenic binding site on the F glycoprotein due to the substitution of the amino acid serine at position 157. As Mebatsion suggested, such a mutant immunogen could be created from a selection of vaccine strains, including the NDW strain.

Mebatsion and Yusoff do not teach the method of administering the NDW vaccine strain, nor do they teach the dosages appropriate for that strain.

Van Wiltenburg teaches a method of protecting a poultry animal from Newcastle Disease via the administration of the immunogen (NDW vaccine strain) where the dose exceeds ^{10}log 5.5 EID_{50}. Such a dosage would fall within either of the ranges specified in claims 8 or 9. van Wiltenburg stated that "[i]t has been found that live vaccines based on the strain NDW are completely safe and readily efficacious..." This provides an incentive to select the NDW strain from the roughly half-dozen strains suggested by Mebatsion. Furthermore, given the extreme similarity between the present mutant immunogen, referred to elsewhere as p.13, and the NDW strain from which it was derived, one would clearly be motivated to adopt van Wiltenburg's teachings regarding the administration of NDW for the administration of p.13.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success by combining the mutant immunogen ND virus marker vaccine based upon the NDW strain where the mutant immunogen lacks the

antigenic binding site on the F glycoprotein as taught by Mebatsion and Yusoff with the method of protecting a poultry animal with the NDW strain a certain concentration as taught by van Wiltenburg. Moreover, the safety and efficacy of the NDW strain as shown by van Wiltenburg would have motivated one to adopt his teachings.

Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yusoff as applied to claim 10 above, and further in view of Mebatsion.

Claim 10 is drawn to a method of generating a Newcastle Disease virus mutant immunogens by growing Newcastle Disease virus in the presence of a monoclonal antibody (designated mAb 54) directed against the immunodominant A4 epitope of the F glycoprotein, such that the mutant develops and grows in the presence of the monoclonal antibody whereas nonmutants are neutralized by the monoclonal antibody. Yusoff teaches all of these things. Claim 11 adds the limitation that the ND virus is the NDW strain.

Yusoff does not teach the NDW strain of ND virus. Instead, Yusoff used the Beaudette C strain.

Mebatsion also teaches a method of generating of mutant immunogens of Newcastle Disease virus. In particular Mebatsion indicates that the optimal mutant immunogens will be based upon current vaccine strains, including the NDW strain. See

page 8. Impliedly, the reason for selecting such a strain would be its known characteristics as a vaccine including its proven safety and efficacy.

One of ordinary skill in the art would have had a reasonable expectation of success of combining the method of generating a Newcastle Disease virus mutant immunogens by growing Newcastle Disease virus in the presence of a monoclonal antibody directed against the immunodominant A4 epitope of the F glycoprotein as taught by Yusoff with the use of vaccine strains such as the NDW strain as taught by Mebatsion to achieve a Newcastle Disease marker vaccine that exhibits the general characteristics of the vaccine strains including their safety and efficacy.

Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Allowable Subject Matter

The prior art does not teach or suggest SEQ ID NO: 2. Therefore, claim is 14allowable over the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thursday, April 22, 2004

Shanon Foley
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